PAIN Clinical Updates

INTERNATIONAL ASSOCIATION FOR THE STUDY OF PAIN®

Volume XIII, No. 6 December 2005

UPCOMING ISSUES

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Visceral Pain

Magnitude of the Problem

The recent growth in interest by researchers, clinicians, and the public in pain originating from internal organs reflects an important paradigm shift. In the past, viscera were considered insensitive to pain, mostly because their responses had not been tested with adequate stimuli. It is now clear that pain from internal organs is widespread and that its social burden may surpass that of pain from superficial (somatic) sources. Credible epidemiological data point to its wide prevalence in various medical conditions, whether organic or dysfunctional, in which it is manifest in acute, recurrent, or chronic form. Moreover, the relatively recent finding of crosstalk between different visceral afferents may account for the apparent diffuse enhancement of pain perception in patients with multiple painful visceral conditions.[1-2]

The impact of visceral pain is now well established, as several examples demonstrate. Myocardial ischemia from atherosclerosis, the most frequent cause of cardiac pain, is the most common cause of death in the United States.[3] Kidney and ureteral stones produce urinary colic, one of the most intense forms of pain that a human being can experience. The prevalence of such stones has continuously increased during the 20th century, reaching values of over 20% in developed countries.[4-5] Irritable bowel syndrome (IBS), a dysfunctional condition causing recurrent attacks of abdominal pain, has been estimated to affect 25% of the population in many countries and accounts for 40–50% of all gastroenterologic consultations worldwide.[6-8] Dysmenorrhea, provoking intense and often disabling abdominal/pelvic pain at every cycle, is estimated to affect more than 50% of menstruating women, with 10% being forced to abstain from work for a few days each month and at least 30% reporting no improvement with medical treatment.[9-11] Given the high prevalence of these few conditions, the large number of internal organs in the human body, and the numerous painful conditions that can affect each organ, it is not difficult to appreciate the global burden of the totality of visceral pain.

Although visceral pain symptoms are common, sometimes they herald a life-threatening underlying cause such as myocardial infarction, intestinal obstruction, acute pancreatitis, or peritonitis. Prompt evaluation and specific diagnosis of visceral pain is therefore mandatory,[1,2] but is not always easy because such pain is less well-localized and more poorly described than superficial pain and tends to vary over time. As mentioned, clinical evaluation of visceral pain

Supported by an educational grant from **Endo Pharmaceuticals Inc., USA**

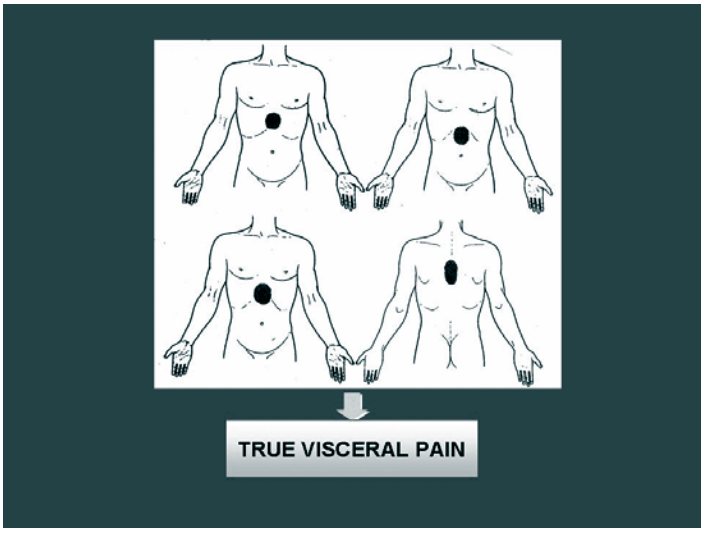

Figure 1. Clinical characteristics that suggest "true visceral pain": midline pain, poorly discriminated, with marked neurovegetative and emotional features, with no hypersensitivity on palpation of the painful area. (Modified from Giamberardino.[56])

may also be complicated by the presence, in the same patient, of concurrent painful conditions in more than one internal organ. In such instances the resulting complex symptoms can be deceptive.[2,13] In-depth knowledge of the variable manifestations of visceral pain is thus indispensable to interpret the elusive clinical reality. While treatises have been written on visceral nociception, this issue of *Pain: Clinical Updates* is intended to clarify for frontline clinicians the various ways in which this symptom presents in different clinical contexts and how it varies with factors such age and sex, as well as to touch upon methods for its treatment.

The Clinical Picture

Visceral pain has a temporal evolution, and in its early stages it can be insidious and difficult to identify.[13] Due to the low density of sensory innervation of viscera and the extensive divergence of visceral input within the central nervous system (CNS), what is called *true visceral pain* is a vague, diffuse, and poorly defined sensation (Fig. 1).[12,14] Regardless of the specific internal organ of origin, it is usually perceived in the midline at the level of the lower sternum or upper abdomen. Whether the origin is from the heart, esophagus, stomach, duodenum, gallbladder, or pancreas, visceral pain in its early phase is perceived in this same general area. Additional stimuli such as local compression applied to this area fail to worsen the pain.[12] True visceral pain may be minimized or overlooked when it cannot be clearly described, other than as a vague sense of discomfort, malaise, or oppression. It is typically associated with marked autonomic phenomena, such as pallor, profuse sweating, nausea, vomiting, changes in blood pressure and heart rate, gastrointestinal disturbances (e.g., diarrhea), and changes in body temperature. Strong emotional reactions are commonly present that include anxiety, anguish, and sometimes even a sense of impending death. Sometimes visceral pathology may manifest principally through vegetative and emotional reactions, with minimal pain and discomfort. A typical example is painless myocardial infarction, which may produce a sense of gastric fullness, heaviness, pressure, squeezing, or choking. These deceptive symptoms may lead to an incorrect diagnosis such as gastrointestinal pathology, especially when vegetative signs such as nausea and vomiting are present.[12] As a general rule, the intensity of visceral pain bears no relationship to the extent of the internal injury.[13,15] Again, this is evident in the example of painless myocardial infarction, which involves death of cardiac muscle, versus angina, which reflects only ischemia without permanent tissue damage.[9] The dissociation between magnitude of injury to internal organs and intensity of pain is a potentially dangerous circumstance that must be kept in mind by the clinician evaluating visceral symptoms. Visceral pain should thus always be suspected when vague midline sensations of malaise are reported by a patient, especially if he or she is elderly.

Further diagnostic problems may arise as visceral pain progresses. Within minutes to a few hours, pain from a visceral organ may be experienced ("referred") at sites of the body wall whose innervation enters the spinal cord at the same level as the

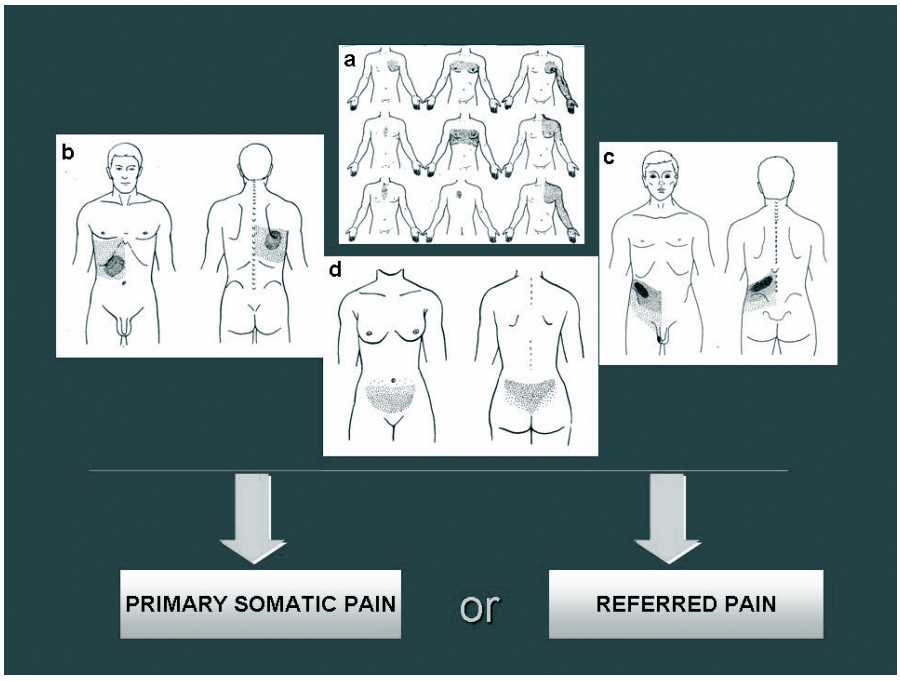

Figure 2. Overlapping clinical presentations of well-discriminated pain localized in the body wall (somatic) with mild neurovegetative signs, constituting either primary somatic pain or referred pain from (a) the heart, (b) the biliary tree, (c) the urinary tract, and (d) the female reproductive organs. (Modified from Giamberardino.[56])

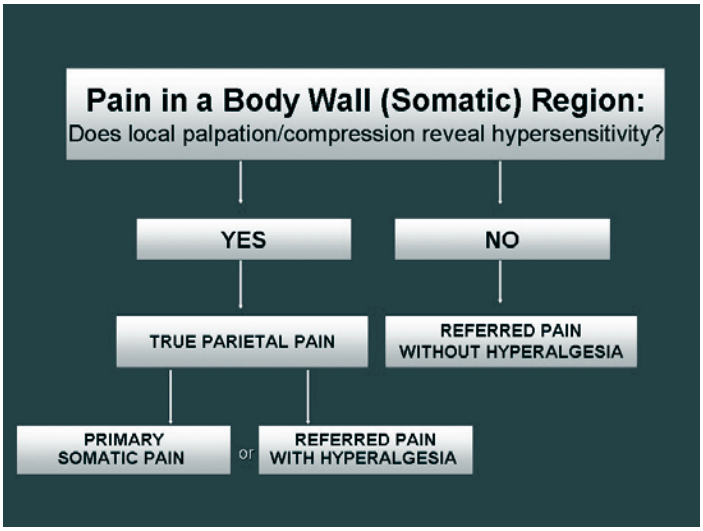

Figure 3. Flow diagram to differentiate referred pain without hyperalgesia from true parietal pain (primary somatic pain or referred pain with hyperalgesia). (Modified from Giamberardino.[56])

innervation from the visceral organ involved. The convergence of visceral and somatic afferent fibers onto the same spinal sensory neurons leads to this misinterpretation by higher brain centers.[14,15] Referred pain is sharper, better localized, and less likely to be accompanied by neurovegetative and emotional signs, and is thus similar in quality to pain of deep somatic origin, from which it needs to be differentiated (Fig. 2). It may be associated with hyperalgesia (i.e., increased sensitivity to nociceptive stimuli and decreased nociceptive threshold) of the tissues in the painful area (*referred pain with hyperalgesia*). Hyperalgesia of referred pain is most frequently confined to the muscle, often accompanied by sustained contraction, but it may extend superficially to subcutaneous tissue and skin when the underlying painful processes are repeated or long-lasting.[2,12,13] An integral part of the initial physical diagnostic examination of a patient with suspected visceral pathology is a search for hyperalgesia in the somatic region to which pain is referred. The absence of such hypersensitivity allows one to categorize the symptom as *referred visceral pain without hyperalgesia*. If local hypersensitivity is present, then one must decide whether it reflects a primary problem of somatic structures or is *referred visceral pain with hyperalgesia* (Fig. 3). At this point, only the global outcome of a detailed clinical history, physical examination, and supplemental laboratory and imaging examinations will allow a definite diagnosis.[2]

The referred hyperalgesia from internal organs is likely to result from a process of central sensitization involving viscerosomatic convergent neurons ("convergence-facilitation"), as shown by electrophysiological data in animal models of the condition.[15-17] It is a prominent phenomenon in patients because it is accentuated by the repetition of the visceral episodes and persists long after the initiating pain has ceased.[18,19] For example, deep tenderness is often evident in the lower abdomen in dysmenorrheic women in the interval between painful menstrual cycles, as well as in corresponding somatic sites in patients who have already passed painful urinary calculosis or have experienced biliary colics in the past.[14,20,21] Referred hyperalgesia from viscera is also often accompanied by trophic changes, typically a thickening of the subcutaneous tissue and some degree of local muscle atrophy. Both of these findings presumably result from viscerosomatic reflexes activated by the massive afferent visceral barrage,[22,23] and both may persist long after the primary visceral problem is in remission.[21] Visceral pain can affect the somatic tissues in the referred area for months or even years.[2,12]

Another clinical expression of visceral nociception is *visceral hyperalgesia* (Fig. 4), an increased sensitivity of an internal organ such that even nonpathological, normal stimuli may produce pain from that organ[24]. Usually the result of visceral inflammation that leads to both peripheral and central sensitization,[1] visceral hyperalgesia is very frequent in the clinical setting. Examples include pain upon ingestion of food or liquids in the esophagus or stomach when their mucosa is inflamed, or pain from a normal degree of bladder distension during inflammatory processes of the lower urinary tract.[2]

A particularly important visceral pain phenomenon is *viscerovisceral hyperalgesia* (Fig. 5), an augmentation of pain symptoms due to the sensory interaction between two different internal organs that share at least part of their afferent circuitry.[2,13] Patients with coronary heart disease plus gallbladder calculosis, for instance, may experience more frequent attacks of angina and biliary colic than patients with a single condition, based upon the partially overlapping (T5) afferent pathways from the heart and gallbladder.[25] Women with both dysmenorrhea and IBS tend to complain of more intense menstrual pain, intestinal pain, and referred abdominal/pelvic hyperalgesia than do women with only one of these conditions. Likewise, patients with dysmenorrhea and endometriosis plus urinary stones have

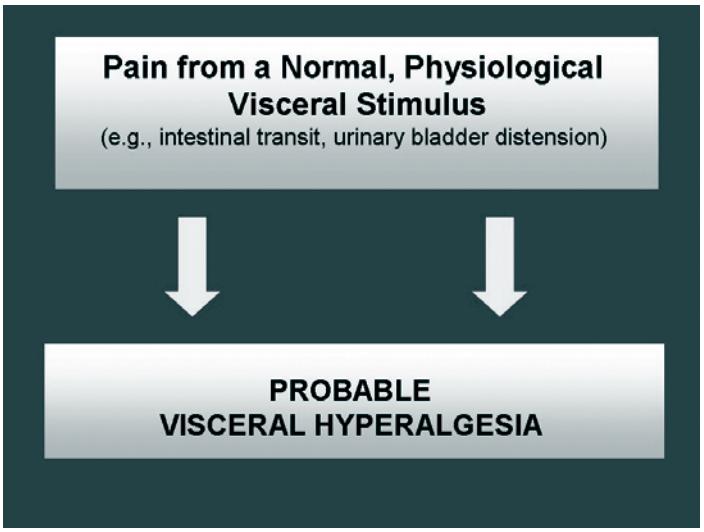

Figure 4. Clinical characteristics of visceral hyperalgesia.

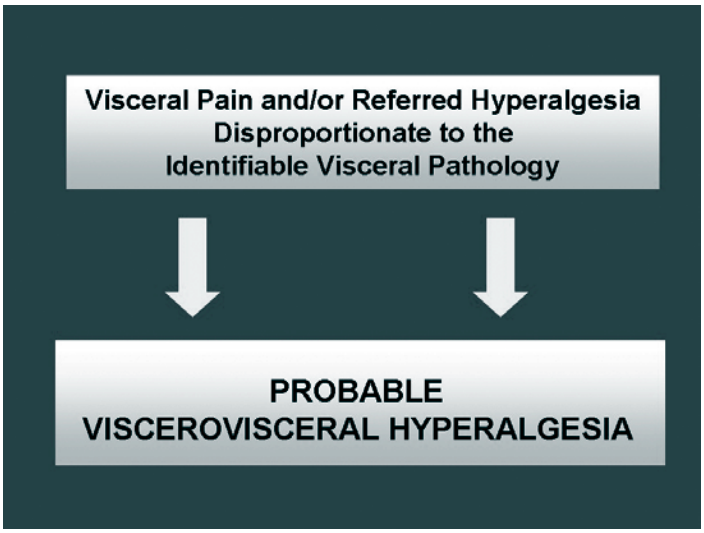

Figure 5. Clinical characteristics of viscerovisceral hyperalgesia.

more intense menstrual pain, urinary colic pain, and referred abdominal and lumbar hyperalgesia as a result of the common sensory pathways (T10–L1) from the uterus, colon, and urinary tract.[26,27] Viscerovisceral hyperalgesia is most likely produced by sensitization processes involving viscerovisceral convergent neurons in the CNS. This phenomenon is receiving increasing attention in medical practice,[28] in which it has been observed that effective treatment of one source of visceral pain (e.g., lithotripsy to eliminate a urinary stone) may improve symptoms from another visceral cause (e.g., dysmenorrhea).[2,27]

Visceral Pain in Older People

The shift toward an older population, especially in developed countries, is well documented. Life expectancy has doubled in the past century, and it is expected that in the year 2050, a quarter of the world's population will be older than 65. This substantial demographic change has provoked a range of problems in medicine and particularly in pain diagnosis and management.[29-30]

Increasing evidence shows that aging substantially affects the way various illnesses may present, particularly for painful processes due to internal pathology. Elderly patients with visceral pain conditions are far more likely than younger adults to present atypically, such as in the direction of diminished intensity of acute visceral pain. This diminished intensity paradoxically occurs despite an increase, with advancing age, in the incidence of pathological conditions that affect the viscera.[29] One example is atherosclerosis, which increases exponentially with age, but without a parallel increase in manifestations of ischemic pain from internal organs. Silent ischemia and painless myocardial infarction both become more frequent with advancing age,[32] so that clinicians should have a low threshold of suspicion to rule out these diagnoses. Retrospective studies have found that about a third or more of heart attacks in adults older than 65 are silent or painless.[33] Other visceral conditions that show an age-related change in pain symptoms and presentation, typically in the direction of reduced or absent pain in older people, are pneumothorax and abdominal complaints such as peptic ulcer, intestinal obstruction, and peritonitis.[29] About 45% of older adults with appendicitis do not have lower-right quadrant pain as a presenting symptom, in contrast with fewer than 5% of younger adults.[34] Visceral pain associated with various types of malignancy is also reported to be less intense in adults of advanced age than in younger individuals.[35]

The pathophysiology of decreased visceral pain sensitivity with aging is far from being completely elucidated, but possible mechanisms may include a lower density of nociceptors, impaired A-delta fiber function, altered serotonin metabolism, increased activity of spinal non-opioid analgesic pathways in older individuals, and also decreased neuronal responsiveness to nitric oxide.[29,31] Also worth noting is the higher prevalence in the elderly of medical conditions such as hypertension or diabetes that are associated with impaired pain perception.[36-38] Thus, elderly patients affected with these conditions may have the highest risk of presenting with painless visceral diseases. These factors should be kept in mind by clinicians, who should be prepared to suspect and pursue the diagnosis of potentially dangerous or life-threatening diagnoses in elderly patients.

Visceral Pain and Gender

Clinical and experimental research indicates gender differences in the perception of pain from internal organs. While the nature of these differences is not always consistent across studies, some important generalizations can be made on the basis of the available data.[39]

For gender-specific viscera, women appear more subject than men to manifest a number of "paraphysiological" visceral pains in the course of their life due to the more complex nature of their reproductive function. These pains include recurrent pain from the uterus during the ovarian cycle in their fertile years (if they are dysmenorrheic), labor pain, and postpartum visceral "after pains."[40] Women are also more prone to develop frank "pathological" pains from the same viscera, such as chronic pelvic pain as a result of ascending genital or urinary infections, which are more frequent than in men for anatomical reasons (e.g., the shorter urethra in females).[41]

As regards non-gender-specific viscera, the prevalence of a number of painful pathologies varies between men and women. Some conditions predominantly affect men (e.g., coronary heart disease, with a mortality rate in those younger than 55 four times that of women), while others are more prevalent in women (e.g., gallbladder disease), mainly because of differences in risk factors between the two sexes (e.g., for atherosclerosis or gallstones) that are linked to both hormonal status and lifestyle.[42-43] Other clinical entities—mostly without a clear organic cause, such as IBS or interstitial cystitis—are more prevalent in women because of a presumed higher susceptibility of females to nociceptive sensitization.[44-45] Gender influences

the nature of pain from the same visceral pathology (intensity, location, and quality) as well as the array of accompanying symptoms. The specific profile of visceral pain appears less predictive in women than men for individual visceral diseases.[46] Sociocultural factors play a crucial role in the experience and report of pain, and they may have different effects on women and men (both as patients and as physicians).[39]

Another important difference between the sexes is that women appear more prone than men to develop viscerovisceral hyperalgesia, as noted above for the nociceptive interaction between the female reproductive organs and urinary tract.[2] This propensity most likely places women at greater risk than men for prolonged episodes of pain from internal organs, especially those in the lower abdomen and pelvis. In addition, since visceral pain is referred to more superficial somatic areas of the body, where hyperalgesia most often develops, women are more likely than men to have extended areas of somatic (especially muscle) hyperalgesia from multiple, concurrent, and recurrent visceral pains.

In summary, current research suggests that visceral pain conditions in women are not only more prevalent and persistent, but also may be more insidious, complex, and difficult to diagnose. In contrast, visceral pain in men tends to be more clear-cut, both in description (e.g., chest pain) and etiology. In addition, physicians commonly belittle algogenic processes of the female reproductive organs because they regard pain from this area as normal.[39] The net result is that visceral pain is often undertreated in women compared to men, and when treated it is given empiric rather than mechanism-based therapy. Early, focused clinical attention on even mild visceral pain in all patients, but particularly in women, may ultimately benefit the quality of life of all afflicted with such symptoms.

Treatment

Treatment of visceral pain proceeds in parallel, both to address underlying pathology, when identifiable, and to alleviate symptoms. The pathology encompasses a large number of conditions in many organs, and its definitive diagnosis and therapy often requires specialist consultation and procedures ranging from angioplasty for cardiac ischemia, to surgery for conditions such as intestinal adhesions, to lithotripsy for urinary stones, or laparoscopic laser ablation of endometriosis.[9] In theory, pain management might be deferred until the origin of the symptoms has been identified, because masking pain may confound the diagnostic process, even to the point of delaying recognition of a potentially life-threatening condition. But in practice, a clear cause of each symptom may never be proven, and prolonged fruitless investigations should cease before new, procedure-related pain has been introduced or psychological problems become insurmountable. Certainly, once a treatable condition has been identified, there is no reason to withhold symptomatic treatment. To the contrary: the more prolonged or repetitive the visceral afferent barrage into the CNS, the greater the risk of long-term sensitization and its consequences such as referred hyperalgesia and trophic changes.[2,13,47]

Symptomatic treatment of visceral pain mainly relies upon pharmacotherapy not only with classic analgesic compounds, but also with agents that, while not analgesic per se, reduce pain in specific circumstances by lessening visceral nociceptive input.[9] The latter include nitrates, which reduce anginal pain by promoting coronary arterial vasodilatation; gastric-targeted histamine receptor antagonists or proton pump inhibitors, which alleviate ulcer or gastritis pain by reducing stomach acidity; and spasmolytics, which relieve pain from obstruction of hollow viscera by interrupting the reflex contraction of the viscus.[12] For referred pain with hyperalgesia, clinical experience suggests that deep infiltration of the muscle layer of the referred area with a local anesthetic[2,13] may be helpful, but this impression awaits confirmation in systematic controlled studies in patients. Nonpharmacological treatments of the pain also play an important palliative role, such as neurostimulation for refractory angina, a technique that has been shown to be effective in several randomized controlled trials.[48,49] Other examples are selective surgical lesions of visceral pain pathways; according to some clinical reports, these would include selective lesions of the dorsal columns in patients with intractable visceral pain.[50,51] The rationale for the latter intervention has been strengthened by preclinical support for the role of the dorsal columns in conducting visceral afferent nociceptive signals.[52,53] Strong evidence from multiple randomized controlled trials supports the use of neurolytic celiac plexus block to alleviate pain and reduce opioid consumption in patients with malignant pain originating from abdominal viscera such as the pancreas.[54] Similar, though less definitive, evidence suggests benefit from other neurolytic blocks of visceral afferent pathways, such as hypogastric block for otherwise refractory pain from rectal or cervical cancer.[55]

Lastly, the substantial and growing clinical and experimental literature on viscerovisceral hyperalgesia offers a rationale to suggest that any treatment plan for pain from a specific internal organ should simultaneously address pathology in other neurally related organs. Such a multitargeted approach may be expected to counter that portion of augmented pain intensity attributable to visceral crosstalk.[2]

References

1. Cervero F, Laird JM. J Neurobiol 2004;61(1):45-54.
2. Giamberardino MA. In: Devor M, et al. (Eds). Proceedings of the 9th World Congress on Pain, Progress in Pain Research and Management, Vol. 16. Seattle: IASP Press, 2000, pp 523-550.
3. Silverman DHS. Curr Rev Pain 1999; 3(4):291-299.
4. Trinchieri A, et al. Eur Urol 2000; 37(1):23-25.
5. Vasavada PV, et al. In: Loeser JD (Ed). Bonica's Management of Pain. Philadelphia: Lippincott, Williams & Wilkins, 2001, pp 1309-1325.
6. Chang L. Aliment Pharmacol Ther 2004; 20(7):31-39.
7. Mayer EA. In: Giamberardino MA (Ed). Pain 2002—An Updated Review: Refresher Course Syllabus. Seattle: IASP Press, 2002, pp 423-429.

8. Russo MW, et al. J Clin Gastroenterol 1999; 29:339-343.
9. Loeser JD (Ed). Bonica's Management of Pain, 3rd ed, Philadelphia: Lippincott Williams & Wilkins, 2001.
10. Wang L, et al. Occup Environ Med 2004; 61(12):1021-1026.
11. Ylikorkala O, Dawood MY. Am J Obstet Gynecol 1978; 130:833-847.
12. Procacci P, et al. In: Cervero F, Morrison JFB (Eds). Visceral Sensation, Progress in Brain Research, Vol. 67. Amsterdam: Elsevier, 1986, pp 21-28.
13. Giamberardino MA. Eur J Pain 1999; 3(2):77-92.
14. Vecchiet L, et al. Pain 1989; 36:289-295.
15. Cervero F. Gut 2000; 47:56-57.
16. Giamberardino MA, et al. Neurosci Lett 1996; 203:89-92.
17. Roza C, et al. J Neurophysiol 1998;79:1603-1612.
18. Giamberardino MA, et al. Pain 1994;56(1):77-83.
19. Vecchiet L, et al. Adv Pain Res Ther 1992; 20:101-110.
20. Giamberardino MA, et al. Pain 1997; 71:187-197.
21. Giamberardino MA, et al. Pain 2005; 114:239-249.
22. Giamberardino MA, et al. Neurosci Lett 2003; 338:213-216.
23. Jänig W, Häbler H-J. In: Gebhart GF (Ed). Visceral Pain, Progress in Pain Research and Management, Vol. 5. Seattle: IASP Press, 1995, pp 311-348.
24. Gebhart GF. Am J Physiol Gastrointest Liver Physiol 2000; 278:834-838.
25. Foreman RD. In: Mayer EA, Saper CB (Eds). The Biological Basis for Mind Body Interactions, Progress in Brain Research, Vol. 122. Amsterdam: Elsevier, 2000, pp 209-221.
26. Berkley KJ, et al. J Neurophysiol 1993; 69:557-568.
27. Giamberardino MA, et al. Neurosci Lett 2001;304:61-64.
28. Giamberardino MA, et al. Pain 2002; 95:247-257.
29. Gibson SJ. In: Dostrovsky JP, et al. (Eds). Proceedings of the 10th World Congress on Pain, Progress in Pain Research and Management, Vol. 24. Seattle: IASP Press, 2003, pp 767-790.
30. Helme RD, Gibson SJ. Clin Geriatr Med 2002; 17:417-431.
31. Moore AR, Clinch D. Ger Biosci 2004; 52:132-136.
32. Stern S, et al. Circulation 2003; 108(14):99-101.
33. MacDonald JB, et al. Age Ageing 1983; 12:17-20.
34. Wroblewski M, Mikulowski P. Age Ageing 1991; 20:90-94.
35. Caraceni A, Portenoy RK. IASP Task Force on Cancer Pain. Pain 1999; 82:263-274.
36. Bierhaus A, et al. J Clin Invest 2004; 114(12):1741-1751.
37. France CR, et al. Pain 2002; 98:101-108.
38. Ghione S. Hypertension 1996; 28:494-504.
39. Giamberardino MA. In: Fillingim RB (Ed). Sex, Gender, and Pain, Progress in Pain Research and Management, Vol. 17. Seattle: IASP Press, 2000, pp 135-163.
40. Holdcroft A. Curr Rev Pain 1999; 2:137-143.
41. Lipscomb GH, Ling FW. Obstet Gynecol Clin North Am 1993; 20:699-708.
42. Caroli-Bosc FX, et al. Dig Dis Sci 1999; 44(7):1322-1329.
43. Chiamvimonvat V, Sternberg L. Can Fam Physician 1998; 44:2709-2717.
44. Doggweiler-Wiygul R, et al. Curr Rev Pain 2000;4(2):137-141.
45. Naliboff B, et al. Curr Rev Pain 1999; 3:144-152.
46. Redberg RF. Medscape Womens Health 1998; 3(5)1.
47. Song SO, Carr DB. Pain: Clin Updates 1999; VII:1.
48. Jessurun GA, et al. Eur J Pain 2003; 7(6):507-512.
49. Diedrichs H, et al. Curr Control Trials Cardiovasc Med 2005; 6(1):7.
50. Gildenberg PL. Stereotact Funct Neurosurg 2001; 77(1-4):169-171.
51. Hwang SL, et al. J Pain Symptom Manage 2004; 27(1):79-84.
52. Palecek J. Physiol Res 2004;53(1):125-130.
53. Willis WD Jr, Westlund KN. Curr Pain Headache Rep 2001; 5:20-26.
54. Eisenberg E, et al. Pain: Clin Updates 2005; XIII:5.
55. Lema MJ. Pain: Clin Updates 1998; VI:1.
56. Giamberardino MA. La lettre d'Institut UPSA de la Douleur 2004; 21:1-8

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